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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

TRANSMITTED VIA FACSIMILE

OCT 31 1997

Richard J. Kogan, CEO
Schering Corporation
1 Giralda Farms
P.O. Box 1000
Madison, NJ 07940

Re:		
	Vancenase	NDA 18-521
	Vancenase AQ	NDA 19-589
	Vanceril	NDA 17-573

WARNING LETTER

Dear Mr. Kogan:

This Warning Letter addresses Schering Corporation's ("Schering's") dissemination of promotional materials concerning Vancenase nasal spray, Vancenase AQ nasal spray, and Vanceril inhaler. The Division of Drug Marketing, Advertising, and Communications ("DDMAC") has reviewed these materials as part of its monitoring and surveillance program. DDMAC has concluded that Schering, in its promotion of these products, has disseminated promotional materials that contain statements or suggestions that are false, lacking in fair balance, or otherwise misleading in violation of the Federal Food, Drug, and Cosmetic Act (the "Act"), 21 U. S. C. §§ 352(a), 331(a) and applicable regulations.

These false or misleading promotional messages were disseminated repeatedly during promotional presentations that Schering termed "interactive scientific teleconferences" or "market research" (i.e., "focus groups").[1] These promotional presentations were conducted for Schering by Palazzole Associates ("Palazzole"). Schering misrepresented the nature of these programs to health care providers as "research" or "interactive scientific teleconferences" rather than as promotional

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[1] The promotional materials discussed in this letter include, but are not limited to the materials disseminated at or for these presentations.

activities by a prescription drug manufacturer. In fact, the promotional nature of these sessions was not disclosed and, indeed, was obscured.[2]

The purpose of market research is, generally, to collect information from a targeted audience. Legitimate focus group research usually provides respondents the opportunity for a fair discussion of information or materials provided by a moderator. However, little such audience discussion was held in the Palazzole-led groups. To the contrary, these presentations were more like "detailing" a group of health care providers by a sales representative. First, the "focus groups" conducted by Palazzole for Schering clearly were vehicles for the dissemination of promotional messages in an effort to persuade the audience. Second, the volume of material presented at these sessions did not permit the participants' thorough review and considered feedback. For example, approximately 37 slides with introductory or technical information were presented during a typical one hour session.[3] Finally, the moderator's responses were in the form of selling messages, and questions asked by the moderator were often rhetorical in nature -- emphasizing the products' selling points -- as opposed to inquiries soliciting the participants' view or opinion.

Furthermore, representations that lead participants to believe that their participation and review of the materials was a "research" activity raises serious concerns. The natural defensiveness by which people process promotional messages was circumvented by the presentation of the messages as "research." It is well established that the perceived source of a message is an important determinant regarding its believability and that material presented as advertising or promotion is processed with a great deal of skepticism.[4] It is also well established that

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2 Physicians were recruited for these promotional presentations by letters requesting the individual's participation in an "Interactive Scientific Teleconference," a "Market Research Focus Group Teleconference,"or a "Market Research Focus Group Dinner Meeting."

3 "Oral Inhaled Steroid Market Research Focus Group."

4 It has been demonstrated that information received from highly credible sources is more persuasive than identical information received from less credible sources. C Hovland & W Weiss, The Influence of Source Credibility on Communication Effectiveness, 15 Public Opinion Quarterly 635 (1951). Consumer surveys indicate that about 70 percent of consumers think that advertising is often untruthful and that they consistently approach advertising with a great deal of

participants in research studies are likely to be highly sensitive to, and compliant with, information presented in a research environment.[5] Materials presented as educational in nature are more fully accepted and integrated into the research participants' personal belief systems than material clearly identified as promotional.[6] Thus, the violative materials presented in a "research" context may have led to a greater and unquestioned acceptance of the messages contained therein.

Videotapes of some of these presentations show physicians participating in the promotional programs conducted by representatives acting on behalf of Schering. These representatives made numerous statements that promoted Schering's drug products as being superior to its competitors' products. DDMAC concludes, from its review of the materials distributed at these sessions and the videotaped records of these sessions, that much of the material provided to participants at these

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skepticism. J Calfee & D Ringold, The 70% Majority: Enduring Consumer Beliefs About Advertising, 13 J. Pub. Policy & Marketing 228 (1994). Surveys among physicians demonstrate that promotional material is perceived as being much less reliable than other independent sources. J McCue, *et al*, Physicians' Opinion of the Accuracy, Accessibility, and Frequency of Use of Ten Sources of New Drug Information, 79 So. Med. J. 441 (1986).

5 Martin Orne concluded that research participants respond to the demands placed on them in the research environment by attempting to be "good" subjects and providing "good" data. M Orne, Demand Characteristics and the Concept of Quasi-Controls, *in* Artifact in Behavioral Research 143 (Robert Rosenthal & Ralph Rosnow eds., 1969). This results in subjects providing the types of responses that they perceive that the experimenters are likely to seek.

6 For example, in one study, identical material was presented to research participants but the source of the material was reported variously as an educational leaflet or an advertisement. Participants who were told that the information came from an educational brochure were better able to answer questions that required them to draw implications from the message. Participants who were told that the same information came from an advertisement, however, simply had better recall of the advertisement's verbatim information. L Morris, *et al*, Prescription Drug Information for Consumers: An Experiment of Source and Format, *in* Current Issues & Research in Advertising 65 (James Leigh & Claude Martin eds., 1984).

promotional sessions was false or misleading in violation of the Act and regulations. The information contained in this material included false or misleading statements or suggestions that Schering's products are superior to competitive drug products. These claims are not supported by adequate and well-controlled studies.-- Furthermore, many of the promotional materials present selected data from a variety of studies in a manner that misleadingly implies that the data were obtained from direct comparisons of the products described. The information also included false or misleading statements or suggestions about the safety and efficacy of competitive products and statements about nonclinical findings suggesting clinical significance when no clinical benefit has been established.[7]

Finally, DDMAC notes that Schering did not submit to FDA the materials it disseminated or presented to health care providers in conjunction with the promotional teleconferences and dinner-time meetings. Such submissions are required by the post-marketing reporting requirements in 21 C. F. R. 314.81(b)(3)(i).

Review of Promotional Campaign

The following discussion of violative promotional activities is not a comprehensive recitation of all of the violations, but merely examples of Schering's false or misleading promotional presentations.

Vancenase

Materials disseminated by Schering for the Vancenase promotional programs contain statements that are false or otherwise misleading. These statements (1) make unsupported claims regarding the safety and effectiveness of Vancenase (Schering's brand of beclomethasone dipropionate nasal spray); or, (2) make unsupported comparisons to Flonase (Glaxo Wellcome's brand of fluticasone propionate). The presentations and materials described below state or suggest that Vancenase is better, more effective, safer, and has fewer, or less serious, side effects than has been demonstrated by substantial evidence.

For example, handouts were given to physicians that presented data from a study in healthy volunteers comparing orally inhaled fluticasone propionate and orally

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[7] Schering's use of pharmacokinetic data (such as differences in half-life) to imply superior efficacy or safety of one product over another is misleading when it has not been demonstrated to be of clinical significance.

inhaled budesonide (the "Grahnen" study).[8] These handouts contained information that suggested or represented that the intranasal form of fluticasone propionate (Flonase, a product of Glaxo Wellcome) has clinically negative effects causing hypothalmic-pituitary-axis ("HPA") suppression in patients.[9]

The "Grahnen" study is not a valid comparison of Vancenase to Flonase nasal spray for several obvious reasons. First, Grahnen administered the test drugs by oral inhalation. This route of administration is completely different from intranasal administration and is not predictive of results after nasal administration. Second, even if the routes were comparable in delivering systemic steroid, the doses of fluticasone propionate used in the "Grahnen" study were 25 to 500 percent higher than the (200 ug/day) total recommended daily therapeutic dose of Flonase nasal spray and thus, may result in a greater impact on HPA axis function than the recommended dose.

Schering also presented promotional materials containing claims that "Once-Daily Flonase is No More Effective for Perennial Allergic Rhinitis as Twice-Daily Vancenase."[10] To support this claim, Schering referred to the "van As" study.[11] This claim is false and misleading because the "van As" study did not compare Vancenase (Schering's brand of beclomethasone dipropionate nasal spray) to Flonase. In fact, the "van As" study was conducted by Glaxo and used Beconase AQ (Glaxo Wellcome's brand of beclomethasone dipropionate monohydrate).

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8 A Grahnen *et al*, An Assessment of the Systemic Activity of Single Doses of Inhaled Fluticasone Propionate in Healthy Volunteers, 38 Br. J. Clin. Pharmac. 521 (1994), cited from Eur. Resp. J. (Suppl. 185: 382) (1994).

9 This representation was made as part of a program entitled "New Guidelines for the Diagnosis and Management of Rhinitis."

10 The representation was made as part of Schering programs to "[o]btain Input from Each Physician Regarding the Protocol for a Proposed International Study Comparing the Safety of Products Used to Treat Patients With Both Allergies and Asthma."

11 A. van As *et al*, Once Daily Fluticasone Propionate is as Effective for Perennial Allergic Rhinitis as Twice Daily Beclomethasone Dipropionate, 91 J. Allergy Clin. Immunol. 1146 (1993).

Vancenase and Beconase AQ are not considered to be therapeutically equivalent products.[12]

Furthermore, Schering presented claims, purportedly based on the "van As" study, that "Vancenase" was superior to fluticasone propionate in producing a lower incidence of sneezing, nasal obstruction, rhinorrhea, and nasal itching at weeks 2 and 4.[13] This claim is misleading. Again, Schering's claims based on this study are false and misleading because Vancenase was not used in this study. In addition, Schering selectively presented ("cherry-picked") the results. Although the study reported results from weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24 and at 2 weeks post-treatment, Schering selected and promoted the results ONLY from weeks 2 and 4. However, based on all of the data, the authors concluded that fluticasone propionate was as effective as the beclomethasone dipropionate monohydrate.[14]

Finally, in its teleconference promotions for Vancenase AQ, Schering referred to the "Ratner study"[15] as one of the references to support its efficacy claims.[16] In a letter dated December 11, 1995, DDMAC had advised Schering that the "Ratner study" does not provide adequate substantiation to support the claim that beclomethasone dipropionate (Schering's Vancenase) and fluticasone propionate have comparable efficacy. In response to DDMAC's letter, Schering advised the Agency that use of promotional materials that used the "Ratner" study as partial support had been discontinued.[17] DDMAC is concerned that Schering again used promotional materials that conveyed or contained violative claims or information based on the "Ratner study."

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12 Approved Drug Products with Therapeutic Equivalence Evaluations, 17th ed. (the "Orange Book"), pages 3-36 - 3-37.

13 "New Guidelines for the Diagnosis and Management of Rhinitis."

14 Van As, supra, at 1151.

15 P Ratner, *et al*, Fluticasone Propionate Given Once Daily is as Effective for Seasonal Allergic Rhinitis as Beclomethasone Dipropionate Given Twice Daily, 90 J. Allergy Clin. Immunol. 285 (1992).

16 This representation was made as part of a Schering program to "[o]btain Input from Each Physician Regarding the Protocol for a Proposed International Study Comparing the Safety of Products Used to Treat Patients With Both Allergies and Asthma."

17 Letter to DDMAC, January 12, 1996.

Vanceril

Materials disseminated by Schering for the Vanceril promotional programs contain statements that are false, lacking in fair balance, or otherwise misleading. Many of these materials contain unsupported comparisons to Flovent Inhalation Aerosol (Glaxo Wellcome's brand of fluticasone propionate).

For example, Schering suggests that Vanceril (Schering's brand of beclomethasone dipropionate) is superior to Flovent when it falsely states that there is an "absence of clinical studies conducted with [Flovent's] marketed formulation [containing 1% lecithin]."[18] In fact, Flovent was studied by Glaxo in formulations containing either 1% or 10% lecithin.

In its review of the Flovent NDA, the Agency concluded that Flovent (1% lecithin) meets statutory standards for safety and effectiveness. This conclusion was based on the review of a pharmacokinetics/pharmacodynamic study and a dose-ranging safety and efficacy study that directly compared the 1% and 10% lecithin formulations. The Agency also considered other clinical data within the NDA that used the 1% and 10% formulations. Furthermore, with respect to safety, the pharmacokinetic and pharmacodynamic comparative study showed no clinical or statistical differences between the two formulations in the pharmacodynamic assessment of the HPA axis effects. In addition, the data available from all sources in the NDA, including the dose-ranging and efficacy study, showed no clinically meaningful differences in the safety and tolerability of the two formulations.

The Vanceril materials also state that "Vanceril... A logical choice versus Flovent in patients inadequately controlled with their existing oral inhaled steroids."[19] This claim is unsupported and misleading. Under this heading, Schering refers to and "presents" data from two randomized trials. However, these trials compared Vanceril to Azmacort (Rhone-Poulenc Rorer's version of triamcinolone acetonide) and placebo. Vanceril, Azmacort, and Flovent are distinctly different chemical entities (i.e., different drug products). Data comparing Vanceril to Azmacort do not support claims comparing Vanceril to Flovent. Thus, these data do not support Schering's claim that Vanceril is a logical choice compared to Flovent. Furthermore, in these materials, Schering cited to a review article in further support

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[18] "Oral Inhaled Steroid Market Research Focus Group."

[19] Id.

of its promotional comparative claim (the "Johnson" article)[20]. This article is a pharmacodynamic and pharmacokinetic review of inhaled glucocorticoids, and does not support Schering's claim comparing Vanceril to Flovent.

Conclusions and Requested Actions

Schering's activities have resulted in the dissemination of false and misleading information about its drug products Vancenase nasal spray, Vancenase AQ nasal spray and Vanceril inhaler. Accordingly, Schering should propose an action plan, including the mailing and publication of a "Dear Healthcare Professional" letter, in order to disseminate corrective messages about the issues discussed in this letter to all health care providers, institutions, and organizations who participated in these programs or otherwise received the violative messages.

This action plan should also include:

A. The immediate cessation of dissemination of all materials: (1) that state, suggest, or imply that any of Schering's drug products are superior, or the drug of choice, unless such claims are supported by substantial evidence; or, (2) that contain false, misleading, or unbalanced claims of the type discussed in this letter.

B. A written statement of Schering's intent to comply with "A" above.

C. The dissemination, within 15 days of the date of this letter, of a message to all Schering sales representatives and marketing personnel involved in the marketing and sales of Vancenase nasal spray, Vancenase AQ nasal spray and Vanceril inhaler, instructing them to immediately cease dissemination of all promotional materials and messages discussed in this letter and providing each person with a copy of this letter.

Finally, DDMAC has concluded that the formats used to disseminate the violative materials described in this letter are likely to have led to greater acceptance by the audience because the audience was not advised of the promotional intent of the communications. Consequently, DDMAC believes that, as part of the action plan, Schering should correct these violative messages by also delivering remedial messages about the products named above in communication formats with similar

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[20] Id.; M Johnson, Pharmacodynamics and Pharmacokinetics of Inhaled Glucocorticoids, 97 J. Allergy Clin. Immunol. 169 (1996).

impact. Thus, we invite you to meet with us in the near future to discuss our concerns and a corrective campaign.

Schering's action plan and "Dear Healthcare Professional" letter should be submitted to DDMAC for approval. After such approval, the action plan should be implemented as soon as possible.

The violations discussed in this letter do not necessarily constitute an exhaustive list. We are continuing to evaluate other aspects of Schering's promotional campaign for its drug products and we may determine that additional remedial measures will be necessary to fully correct the false or misleading messages resulting from Schering's violative conduct.

Schering should respond to this letter no later than August 15, 1997. If Schering has any questions or comments, please contact Norman A. Drezin, R.Ph., J.D. or Lesley R. Frank, Ph.D, J.D. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17B-20, 5600 Fishers Lane, Rockville, MD 20857. DDMAC reminds Schering that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID # 4632.

Failure to respond to this letter may result in regulatory action, including seizure or injunction, without further notice.

Sincerely,

Minnie Baylor-Henry

Minnie Baylor-Henry, R.Ph., J.D.
Director
Division of Drug Marketing,
Advertising, and Communications